Ultrasound assessment of carotid plaques over time

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Duplex ultrasound, a useful tool to assess carotid plaque characteristics

In approximately 15–20% of the cases, stroke results from embolisation arising from atherosclerotic plaques of the carotid bifurcation or of the internal carotid artery [1, 2]. Atherosclerosis is a progressive disease characterised by the accumulation of lipids and fibrous elements in the large arteries [3]. Advanced lesions contain lipid-rich necrotic debris and smooth muscle cells. Fibrous lesions typically have a fibrous cap consisting of smooth muscle cells and extracellular matrix that surrounds and encloses the lipid-rich necrotic core. As the plaque progresses, it may exhibit calcifications, ulcerations at the luminal surface and haemorrhage which is presumed to result from small vessels that grow into the lesion from the adventitia of the blood vessel wall [4, 5]. The main mechanism of stroke is thought to be embolism from a fissured or ruptured plaque. Recent pathological studies of postmortem and arterectomy specimens have demonstrated that plaque vulnerability is related to the size of the atheromatous core, the thickness of the fibrous cap and inflammation within the cap. Unstable plaques usually have a thin fibrous cap with a necrotic core situated near the surface. The position of the core and the local thinning of the cap may therefore predispose to rupture which then exposes the thrombogenic atheroma to circulating blood, thus initiating thrombus formation that may lead to thromboembolism and subsequent ischaemic stroke [6, 7].

Duplex ultrasound (DU) is a useful tool for assessment of degree of stenosis and for the characterisation of plaque structure. Degree of stenosis is usually quantified according to three distinct criteria including peak systolic velocities recorded within the jet of the ICA stenosis, the ratio between peak systolic velocities in the ICA and the common carotid artery (CCA) and measurement of stenosis diameter and surface, respectively in a longitudinal and an axial plane [8, 9]. In the longitudinal plane, the measurements may be performed according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) or to ECST (European Carotid Surgery Trial) criteria. Some centers also apply the Common Carotid artery method (CC). The three methods use a ratio between the diameter of the stenosis at the level of the carotid bulb and respectively the distal part of the internal carotid artery considered as normal (NASCET, fig. 1 A/C), the presumed normal diameter of the artery at the level of the carotid bulb (ECST, fig. 1 A/B) and the distal part of the common carotid artery (CC, fig. 1 A/D). ECST and CC methods are usually considered more appropriate for DU because for anatomical reasons the distal part of the internal carotid artery may be sometimes difficult to explore. Degree of stenosis of 70% NASCET corresponds to 85% ECST or CC.

When following a patient over time with carotid stenosis, we have to establish whether a progression is present. The latter is usually defined as an increase of the stenosis of the ICA of 50% or more for ICAs with less than 50% baseline lesion, or as an increase to a higher category (from the 50–69% to the 70–99% category) if the baseline stenosis is 50% or more [10]. Further, three main parameters constitute the basis of plaque morphology classification and include plaque echogenicity, varying from anechogenic through mixed forms to hyperechogenic, plaque texture defined either as homogeneous or heterogeneous and reflecting the distribution of the grey-scale levels in a given area of the plaque and plaque surface defined as smooth and regular, mildly irregular in case of height variations on the contour of the plaque between 0.4 and 2 mm or ulcerated. Ultrasonographically an ulceration corresponds to an irregularity or break in the surface of the plaque which has to be visualised on 2 different planes. Ulcerations must meet 3 criteria: the recess is at least 2 mm deep and 2 mm long, it has a well defined wall at its base and it demonstrates an area of reversed flow (without analysing frequency) within the recess or a zone of low flow signal at the level of the recess [11–13].

What factors are associated with the risk of subsequent stroke?

Although the degree of stenosis constitutes an important determinant for the risk of subsequent stroke, several studies have in fact demonstrated that plaque morphology also...
plays an important role in the pathogenesis of symptomatic carotid disease [13–16]. However, while a number of characteristic features of plaque morphology, including echogenicity, texture and surface, have been associated with an increased subsequent risk of cerebrovascular events, it is not known which one of these different parameters is actually the best predictor of such events. Furthermore, it is known that an important interaction exists between all the different plaque components. For instance, homogeneous plaques tend to have a more regular surface than heterogeneous ones [12, 13]. Also, a higher degree of carotid stenosis is more likely to be associated with heterogeneity [12].

**Carotid plaque progression**

Progression of carotid stenosis is considered as a risk factor for stroke or TIA [17]. Liapis and colleagues reported an annual risk of stroke or TIA of 3 and 5.6%, respectively in patients with a progressive stenosis versus 0.5% and 1.7%, respectively in patients whose lesions did not progress [18]. The reported incidence of carotid artery stenosis progression ranges from 4 to 29%, and in several large series the estimated annual incidence of disease progression ranged from 1.5 to 7% [18, 19]. In a study including 230 patients with asymptomatic carotid stenoses, Carra and colleagues showed that the major predictors of the risk for cerebrovascular events were the progression of the carotid lesion, an irregular surface and a non-homogeneous echographic appearance. Progression of the degree of stenosis was the parameter that correlated most closely with the development of new neurological symptoms. Also, most of the time, lesions that progressed modified their echographic pattern from homogeneous to non-homogeneous and more frequently presented an irregular surface [14]. In another study it could be further demonstrated that plaques with a low echogenicity were more prone to progress. In fact, Liapis and co-workers followed 442 arteries with various degrees of stenosis, with the use of DU every 6 months, over a 12-year period [18]. The significant results were the occurrence of symptoms related to the carotid artery and progression related to the degree of stenosis. In regard to clinical presentation, men (p = 0.07), hypertensives (p = 0.07) and patients with anechogenic (echolucent) plaques (p = 0.09) showed a trend toward a higher frequency of stroke in their history. During the follow-up period, neurological events developed in 12.4% of the cases and were associated with severity of carotid disease (p <0.001), history of neurological events (p = 0.02), progression of stenosis (p = 0.002), anechogenic plaques (p = 0.01) and hypertension (p = 0.02). Furthermore, significant progression of the carotid stenosis documented in 18.5% of the cases was more frequent in younger patients (p = 0.09), in patients with coronary heart disease (p = 0.02) and in patients with anechogenic plaques (p = 0.02). Ballotta and co-workers evaluated the rate of plaque progression in the controlateral ICA of patients (n = 599) who had undergone carotid endarterectomy (CEA) and...
were followed up clinically and by DU scan over a 10-year period at 1 month and then every 6 months [10]. ICA stenosis was classified as mild (30–49%), moderate (50–69%), severe (70–99%), or occlusion. End points of the study were the incidence of contralateral disease progression and late neurologic events. Overall, disease progressed in 25.2% of patients (151/599) after a mean follow-up of 4.1 years. Disease progressed in 34.3% of patients with mild stenosis versus 47.9% of patients with moderate stenosis (p = 0.016). The median time to progression was 29.8 months for mild and 18.5 months for moderate stenoses (p = 0.033). The great majority of events occurred in patients with disease progression from moderate to severe stenosis. This prospective analysis showed that disease progression in contralateral asymptomatic ICAs after CEA is relatively common in patients with a diseased ICA at the baseline and supports DU surveillance, every 6 months, in patients with more than mild disease. A baseline lesion was significantly predictive of progression to severe stenosis, and progression from moderate to severe stenosis was strongly associated with neurologic clinical events.

Establishment of scores

In order to overcome the problem of interaction between the different plaque components, various studies focused on the conception of scores. A new ultrasonographic score has been recently reported in a population-based study of 1348 subjects followed for 12 years on average [20]. This score, called the “Total Plaque Risk Score”, included degree of stenosis, plaque surface irregularity, echolucency and texture and turned out to be the most powerful independent predictor of cerebrovascular events in subjects with at least one plaque at baseline. The authors also showed that in comparison with the Framingham risk score alone (age, total cholesterol, HDL cholesterol, smoking, high blood pressure) addition of plaque characteristics significantly increased the prediction of cerebrovascular ischaemic events. Spence and colleagues developed another scoring system based on the total carotid plaque area measured by ultrasound (cross-sectional area of longitudinal views of all plaques seen) [21]. Plaque area progression (or regression) was defined as an increase (or decrease) of ≥0.05 cm² from baseline. Carotid plaque areas from 1686 patients were categorised into 4 quartile ranges: 0.00 to 0.11 cm² (n = 422), 0.12 to 0.45 cm² (n = 424), 0.46 to 1.18 cm² (n = 421), and 1.19 to 6.73 cm² (n = 419). The combined 5-year risk of stroke, myocardial infarction, and vascular death increased by quartile of plaque area: 5.6%, 10.7%, 13.9%, and 19.5%, respectively (p <0.001) after adjustment for all baseline patient characteristics. A total of 1085 patients had ≥1 annual carotid plaque area measurements: 685 (63.1%) had carotid plaque progression, 306 (28.2%) had plaque regression, and 176 (16.2%) had no change in carotid plaque area over the period of follow-up. The 5-year adjusted risk of combined outcome was 9.4%, 7.6%, and 15.7% for patients with carotid plaque area regression, no change, and progression, respectively (p = 0.003). Carotid plaque area and progression of plaque identified high-risk patients.

Computer-aided analysis of plaque characterisation

The operator-dependant and subjective method of visual plaque characterisation has been a major concern in recent years due to a rather poor inter- and intraobserver agreement [22]. Therefore new methods have been created using a computer-aided analysis providing a more quantitative and more objective as well as a more operator-independent assessment of plaque echostructure. Recent ultrasound studies based on a computerised measurement of the grey-scale median (GSM) value of the carotid plaque demonstrated that a low GSM value, reflecting hypoechoic lesions, was associated with an increased risk of cerebrovascular events and represented a good predictor of carotid plaque behaviour [23–26]. However, although characterisation of the internal structure of the plaque by computer-assisted image analysis correlated closely with clinical symptoms in most of the studies, conflicting results have been obtained so far regarding the association between the computerised analysis of the plaque and the corresponding histopathological findings [27–29]. In fact, as GSM analysis represents a median

### Figure 4
Increase of plaque echogenicity over time (from 2009 to 2011); note the regression of the total plaque area. The change is obtained with statin therapy (atorvastatine 40 mg) in an otherwise normocholesterolemic patient.

### Figure 5
Decrease of plaque echogenicity over time (from 2007 to 2010) and progression of degree of stenosis. The gray median scale (GSM) values decrease from 41 to 0, reflecting the change in echogenicity.
value of the whole atherosclerotic area, it may not necessarily reflect the presence of particular regional components in particular of the surface of the plaque. Another recent method developed first in Japan is the integrated backscatter (IBS), calculated as the average power of the ultrasound backscattered signal from a small volume of tissue [30]. Correlation with histopathological specimens was rather fair, regarding sensitivity (85%) and specificity (91%) to identify various plaque components. Echolocent carotid plaques presented low IBS values whereas more echogenic plaques, higher IBS values.

**Influence of treatment on plaque characteristics**

Several studies have evaluated the effect of treatment and in particular the influence of statins on plaque morphology. All studies showed slower progression, remodelling and even plaque regression after statin administration, although the type, dosage and duration of treatment varied significantly between the different studies [31]. Also, the clinical significance of the attributed changes in carotid plaque morphology remains unknown. Furthermore, it is not clear whether statins act mainly through their effect on LDL levels or whether there is rather a separate pleiotropic action on the carotid plaque. In one review, including 17 studies evaluating the effect of statins on plaque morphology, Makris and co-workers found that intensive therapy had a more pronounced influence on plaque characteristics; however, this was mainly obtained by maintaining low LDL levels [31]. Spence et al., on the other hand, showed in a large prospective study including 4378 patients that plaque progression or regression was independent of plasmatic LDL levels [32]. As plaque echogenicity is a strong predictor of subsequent cerebrovascular events, it has been used as a target in various studies. In one study including 81 hypercholesterolemic patients with carotid atherosclerotic plaques, evaluation of echogenicity of the largest plaque was performed in each patient by DU with IBS analysis [33]. All patients underwent dietary modification, 40 patients with statins (16 with simvastatin, 10 mg/day, and 24 with atorvastatin, 5 mg/day) and 41 without statins. The results showed that statin therapy significantly increased carotid plaque echogenicity in hypercholesterolemic patients.

The 4th figure illustrates the example of change of plaque echogenicity over time with concomitant regression of plaque area. This modification was obtained under statin therapy in an otherwise normocholesterolemic patient (fig. 4). Future studies using echogenicity as an endpoint should therefore evaluate whether patients presenting carotid plaques may benefit from statins independently of their cholesterol values. On the other hand, what would be the most appropriate treatment, if the plaque does not react to statin therapy, even at high doses? Whether there is a benefit of a more aggressive approach, such as surgery, in patients with hypoechoic carotid plaques but with low degree of stenosis and unresponsive to statin therapy, remains a matter of debate and should also be further evaluated in prospective studies.

**Conclusions**

DU is a valuable tool to assess changes of atheroma over time. In fact, several plaque characteristics are associated with an increased risk of cerebrovascular events, including degree of stenosis and its progression, low echogenicity, heterogeneity of the plaque and surface irregularity. It is not known, however, which one of these different parameters is actually the best predictor of such events. New ultrasonographic scores, taking into account all the different plaque characteristics, have recently been established and may constitute a potential aid for risk stratification. Furthermore, several computer-aided programmes have been created in recent years in order to provide a more quantitative and more operator-independent assessment of plaque echostucture by means of DU. Intensive medical therapy, in particular with statins, contributes to slower progression and modification of some of the high-risk plaque features, therefore it becomes more and more important to target treatment not only for the risk factors but also for the different “high risk” characteristics of the carotid plaque.

**Key-words:** carotid plaque, ultrasound, progression, echogenicity, plaque surface, degree of stenosis

**References**


